# Episode 82: Gabapentin and Pregabalin - Effectiveness, Trends and Toxicity



**Transcript**

Hi everyone, welcome back to the Tox Lab.

I'm Rebecca.

And I'm Rob.

This week, we're gonna be taking a look at a class of drugs that started off as one thing and then suddenly became something very, very different in terms of how they used at least. And this is a story we see in drug development and drug history, don't we?

Yeah. There's been quite a few big name of drugs that started off as something and became something else. And I'm thinking, what are the big ones?

Viagra?

Yeah.

Absolutely classic. Started off life, really helping chest pain, turned into that absolutely famous blue pill that men of a certain age may need.

Minoxidil is another one. So this was originally developed as a blood pressure med. But hair growth was a surprising side effect. So it's now used as a hair loss drug. And that's a very different change of career, right?

Yeah. We talked before about TB drugs and how they made people cheerful. And that was how monoamine oxidase inhibitors were discovered. And so drugs often get developed for one thing and then see new life as another. And there's a couple of reasons for this. Once you've done safety trials of a drug, it's easier to find a new use for it than it is go through safety trials again. And so if drug companies can repurpose a drug for a new reason, there is often a financial incentive to do so. But this week we're gonna be looking at gabapentinoids, two drugs in particular, pregabalin and gabapentin. And these have become really synonymous with pain management and are prescribed widely as we'll go into. But interestingly, they actually started life out as anti-epileptic drugs. Before we dive into today's episode, if you wanna stay up to date with our content, you can find us on Instagram at @the_tox_lab. We'll have a page on LinkedIn and we're fairly active on there. And for those of you who don't use social media but still wanna get in touch with episode suggestions or comments about episodes, you can check out our new website at thetoxlab.co.uk. And apologies for those who did try and send messages on the website and were getting blocked. We were notified of an issue with the website which we believe is now resolved. So you should be able to send us messages. And very recently we did our first live stream, didn't we?

Yes, we did. And that was a lot of fun sitting there unpacking the EUDA drug report live.

It was really, really good. Thank you to everyone who tuned in and who commented whilst we were doing the stream. It made it a lot of fun. And it's definitely something we're up for doing again.

Absolutely, I had a lot of fun doing that stream. So yeah, we will definitely be back doing more of that. But yeah, thank you to everyone who tuned in and made that more of a thing than just us talking. Because that was really what made it. And for those of you who didn't catch it live, it is up on YouTube if you wanna go check it out. And at some point we will be putting it up on our podcasting platforms. We just got to do a little bit of editing but it'll be up soon, hopefully.

So gabapentin and pregabalin, gabapentinoids. These are really odd drugs because their name says they're one thing and their activity says a different thing. So the story of gabapentinoids starts with gabapentin.

That was the OG gabapentinoid. And it's structurally very similar to GABA. And I think the logic was that it would act like GABA on the GABA receptor. And originally developed actually in the 70s as an anti-epileptic. And eventually did see approval in the 90s. And what was interesting about gabapentin was it was initially approved as an anti-epileptic but actually saw a change in life to being used in pain management. And then later on in the history of gabapentinoids in the 2000s, pregabalin came along and pregabalin was chemically very similar to gabapentin, slight structural changes. And this is a more potent version. It had better bioavailability and we'll maybe look at that in a little bit more detail later. And again, originally saw use as an anti-epileptic but again started to see use in pain.

Now, as I hinted at, the name is a little bit misleading. The hope was when they developed these compounds that they'd act like GABA and act on the GABAergic neurons, the neurons that work to slow the brain down. And actually it turned out they've got a completely different mode of action. They actually work on the calcium channels of the excitatory neurons. So they bind to the alpha two delta subunit of these calcium channels and they prevent calcium going into these excitatory neurons. Calcium influx is essential for the neurotransmitter release. So if you reduce the calcium influx, you reduce the neurotransmitter.

And we're talking about excitatory neurons. So less excitation, brain ultimately slows down.

So they have a similar effect. They slow the brain down but actually in a sort of opposite way to what we thought they were going to.

They don't increase the break.

They slow down the accelerator. This was the logic for their use as an anti-epileptic. But this is also where their role in certain types of pain came from. So gabapentin does have a lot of approved indications for use. And these include neuropathic pain, partial seizures, restless leg syndrome, alcohol withdrawal, anxiety and tremors. pregabalin is also approved for these uses but has a couple of additional uses including treatment for fibromyalgia and painful diabetic neuropathy which is one of its major uses. And this sort of pain that they're indicated for, they're what we call neuropathic pain.

Yeah, so it's pain that derives not because there is something specifically inflammatory going on that is leading to the pain sensation but rather there is something going on on a nerve level that's leading to this sensation of pain. Slows down that calcium influx into these nerves and essentially calms the nervous system down. And so prescribing patterns is one of those areas that's come under a lot of scrutiny with regards to the gabapentinoids. And this first study looks at the patterns of prescribing of these drugs. So this paper looks at prescribing patterns of both pregabalin and gabapentin in a chronic pain clinic in Houston, Texas over a period of a year. So it covers May, 2023 to the end of April, 2024. And they did this by retrospective chart review. And the patients of interest were those who were prescribed either of these drugs for chronic pain over that study period. And they had 2,395 patients who identified who were receiving care for chronic pain. 20% of this cohort would prescribe gabapentin and 10% would prescribe pregabalin. And it seems in this paper and in a lot of the others

I've looked at, gabapentin seems to be slightly favored. And this might be the result of physician experience, what patients can tolerate. And in the US, gabapentin isn't classed as a controlled substance, so can be more readily prescribed, which might also be one of the reasons for the differences that are seen. So we're looking at differences in side effects. The side effects of gabapentin are often associated with the nervous system, dizziness, excessive drowsiness, or ataxia are quite commonly reported side effects. And while gabapentin is effective at treating neuropathic pain, there does seem to be a higher incidence of these side effects when you're comparing it to a placebo. So there is that trade-off of pain management versus side effect profile. And pregabalin side effects are thought to be more pronounced with dizziness and excessive drowsiness occurring most frequently. And pregabalin can also lead to euphoria, which has sought to correlate with its risk of abuse. And both pregabalin and gabapentin increase the risk of suicidal thoughts. And a population cohort study in Sweden showed that gabapentinoids were associated with increased suicidal behavior and deaths from suicide. It's important to point out this is a correlation, not a causation.

Yeah, of course. We don't know for sure that they lead to that. But there is at least a plausible reason in perhaps disinhibition.

Yeah. In the same way of other drugs conducive. The difference between gabapentin and pregabalin is quite interesting. And it seems to be, we think, related more to its bioavailability. So gabapentin at higher doses isn't so readily absorbed. There is sort of a ceiling effect on absorption, whereas pregabalin is more readily absorbed from the GI tract and more readily crosses the blood-brain barrier. And we think that's why this may be seen a bit more in misuse settings. So this was a single center study looking at a pain clinic and a massive chunk of the patients, 30% in total, were on a gabapentinoid.

Presumably, there's not much overlap. Presumably, it's not like some of them were gonna be on both. I don't think they covered whether anyone was prescribed both. I'm assuming they're prescribed one or the other rather than both. My understanding is in general, they're not prescribed together. So a huge number of patients, and this is one clinic, but lots of patients around the world are prescribed these drugs for pain. How good is the evidence for their use in this way?

So if we've talked about gabapentinoids are being increasingly used for pain management. So in the US in 2021, there were 70 million gabapentin prescriptions and 6.5 million pregabalin prescriptions. And interestingly, approximately 83% of gabapentinoid prescriptions are for off-label pain management. So not necessarily that typical neuropathic pain or the peripheral diabetic neuropathy pain that pregabalin is often frequently prescribed for. And there is a little bit of background to this that we probably need to touch on. Many people may be aware of the use of opioids in the US for chronic pain. Big thing around the time where these drugs started to see development. And as we've cut back on opioid prescribing, because we've realized that they are actually quite harmful, long-term opioid use in the context of chronic pain, the gabapentinoids in a way kind of came in and replaced some of these opioid prescriptions. And that's one of the reasons why I think there's a lot of off-label pain use, because sometimes these patients were on opioid prescriptions.

Yeah, and pain management, especially in chronic pain can be really challenging. Like paracetamol, for example, doesn't really help in severe pain.

Nonsteroidals come with their own side effects, as do opioids, and so gabapentinoids have kind of been brought up to fill a little bit of that gap. And they're often initiated for multimodal analgesia in acute and chronic pain patients, in patients with postoperative and neuropathic pain. And half of these patients are being discharged from the hospital with a gabapentin prescription. And I think when you look at that sort of stat, that's in stark contrast to the actual on-label approved use in diabetic

neuropathy.

Yeah, and with that switch of trying to reduce opioid prescriptions, gabapentinoids were added to the CDC guidelines in 2016 for treating chronic neuropathic pain.

Chronic neuropathic pain.

Yeah.

Not chronic pain in general, which is not the same thing, yeah. But are gabapentinoids really that good at treating chronic pain and chronic neuropathic pain? There are a large number of randomized control trials showing no benefit in using gabapentin for treating diabetic peripheral neuropathy. And there was a Cochrane review of gabapentin for painful diabetic peripheral neuropathy, which showed 38% of participants had at least 50% pain relief with a dose of 1,200 milligrams of gabapentin compared to placebo.

But adverse effects were really common. So again, there's this trade-off of pain management with the side effect profile. gabapentinoid use in off-label conditions show negative or minimal improvements in pain management. And evidence shows it should not be used for low back pain or radiculopathy, which is when a nerve root in the spine is compressed, pinned, or inflamed. And pregabalin is also shown to be ineffective for chronic sciatica with an increase in the adverse effects that are seen. So there does seem to be a bit of controversy as to whether these drugs are useful in a lot of the conditions they're prescribed for. And in my day-to-day experience of being a human being, I often come across people who are on these drugs for things like sciatica.

Yeah. And it's interesting because these people are clearly in quite a lot of pain and will take anything to try and help resolve the issue. But this evidence seems to suggest there may be not as helpful as we once thought. With the use of gabapentinoids, there are also quite a few adverse effects that might make them less desirable. Meta-analyses showed dose-dependent adverse effects with up to a third of patients experiencing dizziness or excessive drowsiness. And gabapentinoids have also been shown to increase risk of falls when combined with opioids. In 2019, the FDA warned about central nervous system depressant co-use and the risk of fatal respiratory depression. And interestingly, most clinical trials for FDA approval of gabapentinoids excluded their co-use alongside central nervous system depressants that hasn't really been factored in. The risk of opioid overdose has been shown to increase sevenfold with concomitant and gabapentinoid use. And it's also been shown to significantly increase the risk of COPD exacerbations in patients with COPD. And the interaction of gabapentinoids with opioids is quite an interesting one. So the general feeling is that they seem to increase the effect of opioids.

They have this modulatory effect. And so the theory is that if you add in a gabapentinoid, you don't need so much opioid or people are perhaps misusing opioids to get more of an effect. And also people talk about using gabapentinoids to help with withdrawals from opioids. Amongst people who use drugs, actually there is a perception of some overlap. But pharmacologically, we can't really explain that. They don't have an effect on the mu opioid receptor. The only common pathway is that they seem to have a general central nervous system depressant effect. And so it's thought that their effect is not through actually making opioids have more of an effect, but rather it's just a general dampening on the brain on top of the opioid. So these drugs have seen a huge rise in their use. And they've moved from these anti-epileptic drugs to these pain management drugs.

Sometimes appropriately, perhaps sometimes inappropriately. And as we've hinted at, they also have misuse potential and they are increasingly seen in misuse contexts. So why don't we now then look at some of the toxicology where these drugs are cropping up and what it means to us as toxicologists?

So this next paper looks at the impact of increased gabapentin use in driving while intoxicated and post-mortem cases in Dallas County. And this covers cases submitted to their toxicology lab between the 1st of January, 2018 and the 31st of December, 2025. There were just over 65,000 cases that were received for analysis during this time. And just under 5% of these were positive for gabapentin, with 87 being driving while intoxicated cases and just under 3,000 being post-mortem cases with the highest number of positive cases received being in 2022. Out of this case data, there were 68 cases where gabapentin was the only drug detected and all but one of these were post-mortem cases. 12 of these had quantitative data with an average concentration being 4,582.6 nanograms per millilitre. When looking at quantitative analysis for all of the cases, this kind of began in 2022. It was available for 1,219 post-mortem cases and 36 driving while intoxicated cases. And the average concentration in post-mortem cases was 8,983.9 nanograms per millilitre. And the average concentration in driving while intoxicated cases was 3,798.1 nanograms per millilitre. And this in itself is interesting actually, isn't it?

Because that's what, four milligrams a litre for the driving whilst impaired and nearly eight, nine milligrams a litre post-mortem. But in the living, the old therapeutic range for anti-epileptic use was up to about 20 milligrams a litre. So these are well in what we would typically see in what we call therapeutic and inverted comma concentrations. I know this is the average, so obviously there's a bit of a range there.

Yeah, they did have quite big ranges on them. And in seven of the post-mortem cases, they couldn't determine an exact quantitative value even with the dilution, it was off the top end of their calibration curve. In driving while intoxicated cases, stimulants with the most prevalent being amphetamine, benzodiazepines with the most prevalent being alprazolam and THC with most commonly identified drugs alongside gabapentin. So in the driving cases, they were always alongside other drugs.

Yeah. And so they were there and they may have been having an effect, but they weren't the sole reason probably for the driving whilst impaired. That makes a bit more sense in the context of therapeutic ranges. In the post-mortem cases, opioids with the most prevalent being hydrocodone, ethanol and stimulants of some methamphetamines were the most commonly co-detected substances. In 155 post-mortem cases, gabapentin was included in the description of the cause of death and most often these were listed alongside other drugs for a toxicity cause of death. And there were 10 cases where gabapentin and only one other drug were implicated. So in this paper, they also include some case examples for both the driving while intoxicated and the post-mortem work. So one of these is an officer responded to a 38 year old potential drunk driver at 2.30 in the afternoon after an attempted U-turn led to the driver becoming stuck in a ditch. Slurred speech, lethargy and difficulty controlling balance was noted upon exit of the vehicle. Field sobriety tests were also performed and the individual had six out of six clues for horizontal gaze nystagmus and eight outs of eight clues in the walk and turn test. He stated he was prescribed various pills for PTSD, depression and bipolar disorder. And his toxicology showed gabapentin at concentration of 8,559.6 nanograms per millilitre alongside carisoprodol at 11.1 milligrams per liter, meprobamate at a concentration of 25 milligrams per liter, doxepin at concentration of 5.3 nanograms per millilitre and 45.8 nanograms per millilitre of desmethyldiazepam. So lots of other drugs alongside the gabapentin and hard to unpick probably the effect the gabapentin on its own was having.

Now you mentioned about how in post-mortem cases they're often detected alongside opioids. And as I hinted at earlier, there is this synergy to a degree in terms of a central nervous system depression between the two types of drugs. Well, this next paper was interesting because it looked at the role of gabapentinoids in death cases, but where there were no opioids. So looking at their role in other cases. This paper is a retrospective study of all deaths in Finland and all cases with a quantitative result in

post-mortem blood for pregabalin and gabapentin between 2016 and 2018. And pregabalin was detected in 594 cases and gabapentin detected in 313 at a concentration above the limit of quantitation, which was 0.1 milligrams per liter. Just under 50% of the pregabalin positive samples had a concentration above the typical therapeutic range, which they equated as 8.2 milligrams per liter, and 34% of the gabapentin cases had a concentration above the typical therapeutic range, which they equated as 20 milligrams per liter. Among all cases of fatal poisoning, pregabalin or gabapentin was implicated in 35% and 22% respectively, and the proportion of fatal poisoning was directly proportional to the concentration of the drug detected in blood. Of the 42 cases where pregabalin was detected at a concentration greater than 41 milligrams per liter, six of these were determined to be unrelated to drug use and opioids were present in all of the cases. Of the 12 gabapentin positive cases with a concentration above 101 milligrams per liter, only one case was not determined to be fatal poisoning because it was deemed a violent suicide. So in post-mortem cases, if you've got a really high gabapentin, my view as it was probably involved.

Yeah. When looking at other drugs detected alongside, opioids were not implicated in 24% of fatal pregabalin poisonings and 20% of gabapentin cases, but where opioids were not detected, alcohol or other drugs were often detected alongside the gabapentinoids. So this brings it back to this idea that on their own, in and of themself, they are not often implicated in fatal cases outside of really extreme situations.

Yeah, so pregabalin was the only drug implicated in the cause of death in two cases where it was detected at a concentration of 52 milligrams per liter and 230 milligrams per liter. So quite a bit above the traditional therapeutic range of 8.2, and for gabapentin, it was the only drug implicated in the cause of death in one of these cases where it was detected at a concentration of 240 milligrams per liter. So again, quite a bit higher than the top end of the therapeutic range. And one thing we do need to mention actually is both of these drugs are cleared by the kidney. So in people who have got renal impairment, they can actually accumulate quite high concentrations of these drugs, even though they're dosing them therapeutically. And that can in itself lead to sedation and lethargy and all of those complications as their blood concentrations are going much higher than typical. So gabapentinoids are an interesting class of drugs, aren't they?

Yeah. Is their career change a success story?

Partially. I think they have their place in certain cases of neuropathic pain, and I think they are effective in certain situations, but I do think they might be being too widely prescribed just to like combat the fact that we don't want to be prescribing opioids as much as we did, but it's not being as effective as maybe an alternative painkiller might be. As you alluded to at the start, pain is hard.

Yeah. People who have got chronic pain have all sorts of reasons. So whether that's neuropathic pain, whether that's chronic back pain because they've got some back issues going on or all sorts of reasons for chronic pain.

People want relief.

Yeah, of course.

And sometimes paracetamol doesn't touch it.

What's next in your arsenal?

Well, opioids, except we know opioids cause all sorts of problems. I mean, short-term opioids, constipation, long-term opioids, real issues with severe health outcomes.

Nonsteroidals, quite good sometimes, but again, carry with them the GI risk, and then you've got to put people on PPIs and they have their own problems. And so I can see why people are turning to these alternative drugs, and they are a very different pathway to the other analgesic drugs. So I can see why they may be trialed in some patients, but I think you're right. A lot of patients I think get put on these drugs really out of desperation.

Yeah.

Because nothing else has worked.

And this may have some benefit.

There may be a partial benefit.

Remember that evidence review wasn't necessarily. It wasn't that they don't help in all situations, as they are beneficial in some areas and for some people, but not so in others.

Exactly, and then carry with them some of the negative side effects like sedation and loss of balance and things like that.

But I think you're right. I think they are a drug that almost certainly has a use, but perhaps is being too widely prescribed. And I think possibly prescribing these and not thinking about alternative solutions, for example, physiotherapy and those sorts of more holistic pathways that might not be being utilized because, oh, we're going to put them on this next med, for example, whereas that could benefit people more.

I see your point. I think it comes back to the fact that pain is not just one thing.

Yeah. Because quite a lot of people with chronic pain won't see any benefit for physio because it's not there's a muscle problem or a joint problem. It's because there is actually a nervous problem. And these are the patients where maybe there might be some benefit to the gabapentinoid drugs. I think the sciatica is an area where that's interesting because there is this plausible reason for why these gabapentinoid drugs might work, but actually the evidence is quite weak. And obviously in sciatica, you have got some inflammation going on alongside the nervous effects. I think the difference between pregabalin and gabapentin is quite interesting. So as we alluded to, really the bigger difference seems to be the bioavailability. And that makes it in a way a slightly pharmacokinetically cleaner drug. But then that seems to carry with it this increased risk of abuse potential, which you don't see so much of with gabapentin. It's interesting in the US that gabapentin is not controlled and pregabalin is.

In the UK, both were controlled. I think that was as of 2021. So I don't know whether that advice has changed.

Things may have changed. And the UK actually scheduled them a little while ago, up until then they were widely prescribed. And then there were some controls put in, brought in as essentially class C drugs. So possession without a prescription is not legal. And when you look at their use in opioids, that's where it also gets interesting because they saw life as an opioid alternative, but actually they then started to be used alongside opioids. And actually that seems to be where some of the respiratory depression risk and potential overdose risk comes in more when they're mixed with these other drugs. So we know they are being misused.

We know they get diverted. We know they get given to people that they aren't prescribed to. Is this because they're drugs that people enjoy taking, that they've got a pleasurable effect? Or is it because there's actually a gap in care for some of these people?

That is a really good point. I think people who are in lots of pain will turn to what they can get hold of. And if that is gabapentinoids, then I can see that being a reason why they're using them. I think for me, the biggest interaction, yes, the interaction with opioids is important. And we see that in the post-mortem cases. But I think the interaction with alcohol is quite substantial. And that's really just due to how many people do consume alcohol.

Not necessarily to a significant dangerous degree, but people like to have a glass of wine in the evening. And suddenly you're on gabapentinoids and you have a glass of wine. That glass of wine hits a lot harder.

Yeah. And then that carries with it all of the risks. Risks of falls, risks of potentially respiratory depression, but also impairment and driving. Somebody could easily be under the limit in inverted commas, but if they're on gabapentinoids and had a drink, that doesn't mean they're good to drive.

Yeah, that's true. It'd be interesting to see with a lot of the data whether when gabapentinoids are being used alongside opiates and benzos, whether those are all being legitimately prescribed to whether they are being sought illicitly. And whether we're necessarily thinking when people are under shared care and you've got lots of different doctors prescribing for lots of different things, are we thinking about the interactions of the drugs that we are giving them? Does there need to be a point where we kind of stop and take a look at the picture as a whole and go, well, maybe if you're being prescribed a gabapentinoid and an opiate and a benzodiazepine, maybe that's not the best idea. And let's try and look for some alternatives that don't necessarily have that interaction.

I think you could be right. I think the challenge here is that they are perceived as being the lighter alternative to both opioids and benzodiazepines. And so they are seen, I think, as a safer option. Although you're right, in combination, perhaps they are making everything a whole lot more toxic. And we've seen this in the life of gabapentinoids in the UK. They started, as we said, as anti-epileptics.

They saw a rise in pain. And then we started to see, particularly pregabalin, the sort of diversion and abuse potential. And then we've seen controls put in place and restrictions on prescribing. You know, GPs coming under pressure not to prescribe these drugs, whereas before they were seen as the safe option. But then where is this all going?

What's the direction of travel? Are we gonna see more gabapentinoids in the future?

Are people gonna use less? I mean, that is a very good question.

Who knows what's around the corner? One thing we haven't touched on, and perhaps we're teasing a future episode here, is there are other gabapentinoids. We focus on the two really widely prescribed ones, but there are some others, including baclofen, which actually doesn't act like a gabapentinoid, and fenibut, which is a bit like Russian gabapentin. And that's a whole nother can of worms actually talking about fenibut. We can definitely talk about that on another episode. And there's even a few niche ones that have occurred as well, novel gabapentinoid alternatives on the MPS scene and things like that. All in all, I think they're a really interesting class of drug. They look like GABA, they don't work like GABA, have an anti-epileptic effect, may be helpful in some nerve pain, probably not helpful in a lot of cases, and seem to have just become normalized as a drug that is prescribed. Well, I hope you've enjoyed listening to us this week as we look at the weird world of gabapentinoids. Do, as always, if you've liked the episode, share it with your friends. Like us on our socials, we'd really appreciate it. Hope you all have an amazing week, and we'll see you next time.

Bye.